सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.



*I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the* ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.**203/Del/03** dated **28th February 2003.***

*Witness my hand this 26th day of March 2004.*

*(S.K. PANGASA)*
*Assistant Controller of Patents & Designs*

0203-03

28 FEB 2003

**FORM 1**

THE PATENTS ACT, 1970
( 39 of 1970 )

# APPLICATION FOR GRANT OF A PATENT

**(See Sections 7, 54 and 135 and rule 33A)**

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 , Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF STABLE PHARMACEUTICAL COMPOSITION OF RABEPRAZOLE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. ROMI BARAT SINGH
b. PANANCHUKUNNATH MANOJ KUMAR
c. VISHNUBHOTLA NAGA PRASAD
d. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

**DR. B. VIJAYARAGHAVAN**
**Associate Director – Intellectual Property**
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10
Fax No. (91-124) 2342027

6. Following declaration was given by the inventors in the convention country:

We, ROMI BARAT SINGH, PANANCHUKUNNATH MANOJ KUMAR, VISHNUBHOTLA NAGA PRASAD, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Romi Singh

(ROMI BARAT SINGH)

b.

(PANANCHUKUNNATH MANOJ KUMAR)

c. V. Nagaprasad

(VISHNUBHOTLA NAGA PRASAD)

d.

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. 686517 dated : 28/12/2002 on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **28TH** day of **February, 2003.**

**For Ranbaxy Laboratories Limited**

**(SUSHIL KUMAR PATAWARI)**
**Company Secretary**

0203-DEL-03

FORM 2

28 FEB 2003

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION
( See Section 10 )

# A PROCESS FOR THE PREPARATION OF STABLE PHARMACEUTICAL COMPOSITION OF RABEPRAZOLE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

*A Company incorporated under the Companies Act, 1956.*

**The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:**

The present invention relates to a process of preparation of stable pharmaceutical composition of rabeprazole.

2 - [[[4 - (3-methoxypropoxy) – 3 – methyl - 2-pyridinyl] - methyl] sulfinyl] - 1H - benzimidazole, hereinafter referred to as rabeprazole belongs to the class of H+ - K+ - ATPase inhibitors. Its intense effect of suppressing gastric acid secretion and an appropriate duration of action makes it useful for treatment of various digestive ulcers.

Rabeprazole is prone to rapid decomposition and discoloration in presence of moisture at neutral to acidic conditions. Conventional stabilizing measures of coating acid sensitive compounds with enteric polymers is however unsuitable for rabeprazole. The acidic functional groups of the enteric polymer react with rabeprazole, leading to its decomposition. A sub coating to separate the core and enteric coat has been recommended and practiced. Decomposition of rabeprazole even occurs during the coating stage, when in contact with coating compositions in commonly used coating equipments such as fluidized bed coater. Hence, other approaches have been used to stabilize rabeprazole in pharmaceutical compositions.

For example US Pat. No. 5,035,899 discloses a method of stabilizing a core containing an acid unstable compound. The unstable core is stabilized by layering the core with a sub coat layer, followed with an enteric coat layer. The sub coat layer or the intermediate layer comprises a water insoluble film forming material and additionally a suspended, water insoluble fine material.

US patent application No. 2002/0039597 discloses a chemically stable pharmaceutical preparation of a benzimidazole type compound wherein the preparation is stabilized by incorporating in the core, at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, amino alkyl methacrylate copolymer E, arginine aspartate, hydroxypropylcellulose and crospovidone.

We have discovered that a core containing rabeprazole may be stabilized against decomposition by incorporating stabilizing amount, of low viscosity hydroxypropylcellulose (HPC-L) and antioxidant(s) into the core.

Hence, the present invention relates to a process of preparation of stable pharmaceutical composition of rabeprazole wherein the core comprises rabeprazole, HPC-L and at least one antioxidant.

The use of HPC-L has proved to be useful in preventing the decomposition and discoloration of compositions containing rabeprazole. Addition of antioxidant(s) has additive effects and improves the stability. Stability of the core containing rabeprazole may further be enhanced with the incorporation of polyvinylpyrrolidone (PVP) in the core. This is clearly evident from the stability data, generated over a period of 1 month at 60°C, listed herein for reference in Table 1 and 2.

HPC-L of the present invention is low viscosity hydroxypropylcellulose. It is conventionally used as a binder in low concentrations. It is available in various grades under the trade names Klucel® E, Klucel® G, Klucel® J and Klucel® L., with viscosity varying from about 5 m. Pas to about 300 m. Pas. In particular Klucel® L can be used.

Antioxidant(s) of the present invention may be selected from lipophilic antioxidants or inorganic antioxidants and the like. In particular butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT). The concentration of antioxidant(s) may vary from about 0.02% to about 0.2% by weight of the total weight of core. Though antioxidant(s) is generally incorporated into the core, optionally the sub coat may also contain antioxidant(s) at concentrations of 0.02% to about 0.5% of the weight of the sub coat.

Polyvinylpyrrolidone of the present invention is a water-soluble polymer, conventionally used as a binder. The average molecular weight of polyvinylpyrrolidone may vary from about 10,000 to about 360,000. It is commercially available in five viscosity grades identified by their K-value: K-15, K-25, K-30, K-60 and K-90, according to viscosity in

ascending order. Polyvinylpyrrolidone with K-value 30 is particularly useful. The concentration of PVP may vary from about 0 .5% to about 5.0% by weight of the total weight of core.

The term rabeprazole as used herein includes rabeprazole and its pharmaceutically acceptable salts thereof. The pharmaceutically acceptable salts include salts of rabeprazole with sodium, potassium, calcium, magnesium and the like. A preferred rabeprazole salt for the purpose of present invention is rabeprazole sodium or rabeprazole potassium.

The pharmaceutical composition of the present invention comprises:

a. a core;
b. a sub-coat layer; and
c. an enteric coat layer

The term core as used herein includes conventionally used cores for oral administration such as tablets, granules, capsules and the like. The core of the present invention comprises rabeprazole, HPC-L and at least one antioxidant. Optionally the core may also contain polyvinylpyrrolidione and other pharmaceutically inert excipients. The core may be prepared by any conventional method known in the art such as wet granulation, dry granulation, direct compression, extrusion-spheronization, moldings and the like.

The sub coat layer of the present invention comprises of a film-forming agent with or without other pharmaceutically inert excipients. Optionally, the sub coat layer may also contain one or more antioxidant(s). The film forming agent of the present invention may be selected from microcrystalline cellulose, carageenan, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol, xanthan gum and the like.

The enteric coat layer of the present invention comprises of an enteric polymer with or without other pharmaceutically inert excipients. The enteric polymer of the present invention may be selected from cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate, hydroxypropyl methylcellulose phthalate (HPMC phthalate), hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L30 D-55, Eudragit® L 100, Eudragit® S 100; and mixtures thereof. Preferred enteric polymer for the purpose of present invention is HPMC phthalate in a concentration of about 50% to about 90% by weight of the total weight of enteric coat layer.

The sub coat layer and enteric coat layer may be applied over the core as solution/suspension of film forming agent or enteric polymer with or without other pharmaceutically inert excipients using any conventional coating technique known in the prior art such as spray coating in a conventional coating pan or fluidized bed processor; or dip coating.

Alternatively, coating can also be performed using hot melt technique whenever possible.

The solvents of the present invention used for coating processes may be selected from methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.

The pharmaceutically inert excipients as used herein may be selected from substances known in the art as diluents, binders, disintegrants, coloring agents, flavoring agents, stabilizers, surfactants, lubricants/glidants, plasticizers and preservatives for pharmaceutical compositions.

The pharmaceutical composition of the present invention may be prepared by adsorbing antioxidant(s) dissolved in a solvent, for example isopropyl alcohol over one of the

diluents, for example mannitol; drying to remove the solvent; blending rabeprazole with HPC-L, antioxidant(s) adsorbed onto the diluent, other diluent(s) (if required), disintegrant(s), stabilizer(s) and binder(s) in geometric progression; mixing with lubricant(s) and compressing into tablet; coating with a sub coat layer followed by an enteric coat layer.

The invention is further illustrated by the following examples but they should not be construed as limiting the scope of the invention any way.

**EXAMPLE 1-8**

The core tablet composition for examples 1-8 is listed in Table 1. The results of the stability evaluation of core compositions for examples 1-8 over a period of 1 month at $60^0$C are listed in Table 2.

Preparation of core tablets of examples 1-3 involved the following steps –

1. Rabeprazole sodium, mannitol, low substituted-HPC, HPC-L and magnesium oxide were mixed together to form a uniform blend.
2. The blend of step 1 was lubricated by mixing with magnesium stearate.
3. The final lubricated blend of step 2 was directly compressed into core tablets using suitable size punches.

On the other hand preparation of core tablets of examples 4-8 which incorporates an antioxidant, involved the following steps –

Table 1. Compositions of the core tablets (Examples 1-8).

| Example No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Rabeprazole Sodium | 20mg | 20mg | 20mg | 20mg | 20mg | 20mg | 20mg | 20mg |
| Mannitol | 118.25 | 113.75 | 106.25 | 113.6 | 113.6 | 113.45 | 107.45 | 105.95 |
| Magnesium oxide | 5mg | 5mg | 5mg | 5mg | 5mg | 5mg | 5mg | 5mg |
| L-HPC | 3mg | 3mg | 3mg | 3mg | 3mg | 3mg | 3mg | 3mg |
| HPC-L | 3mg | 7.5mg | 15mg | 7.5mg | 7.5mg | 7.5mg | 7.5mg | 15mg |
| BHA | - | - | - | 0.15mg | - | 0.15mg | 0.15mg | 0.15mg |
| BHT | - | - | - | - | 0.15mg | 0.15mg | 0.15mg | 0.15mg |
| Isopropyl alcohol | - | - | - | q.s | q.s | q.s | q.s | q.s |
| Polyvinylpyrolidone | - | - | - | - | - | - | 6mg | - |
| Magnesium stearate | 0.75mg | 0.75mg | 0.75mg | 0.75mg | 0.75mg | 0.75mg | 0.75mg | 0.75mg |
| Core Tablet weight | 150mg | 150mg | 150mg | 150mg | 150mg | 150mg | 150mg | 150mg |

Table 2. Results of stability evaluation of core tablets (Examples 1-8) as percentage (w/w) rabeprazole content, over a period of 1 month at $60^0$C.

| Example No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Initial | 99.56 | 99.34 | 99.35 | 99.46 | 99.87 | 99.26 | 99.27 | 99.67 |
| After 1 month at $60^0$C | 70.68 | 79.97 | 90.77 | 82.98 | 83.79 | 84.92 | 87.28 | 92.09 |

1. BHA or/and BHT was dissolved in isopropyl alcohol and adsorbed over mannitol, followed by drying in fluidized bed dryer at room temperature.
2. Rabeprazole sodium, BHA&/BHT coated mannitol; low substituted-HPC, L-HPC-L and magnesium oxide were mixed together to form a uniform blend.
3. The blend of step 2 was lubricated by mixing with magnesium stearate.
4. The final lubricated blend of step 3 was directly compressed into core tablets using suitable size punches.

The above core tablet (Example 1-8) were coated with the sub coat layer and enteric coat layer using the following coating compositions –

**(i) Sub coat layer**

| | |
|---|---|
| Hydroxypropylmethyl cellulose | 26.06 mg |
| Polyvinyl pyrrolidone | 0.53 mg |
| Titanium dioxide | 0.46 mg |
| Ferric oxide yellow | 0.07 mg |
| Propylene Glycol | 3.91 mg |
| Water | q.s. |

**(ii) Enteric coat layer**

| | |
|---|---|
| HPMC Phthalate 55 | 13.04 mg |
| Triacetin | 1.46 mg |
| Talc | 4.09 mg |
| Ferric oxide yellow | 0.02 mg |
| Titanium dioxide | 0.72 mg |
| Acetone | q.s. |

**Procedure:**

A. Coating of core tablet (Example 1 – 8) with the sub coat layer, involved the following steps-

1. Color and titanium dioxide were added in propylene glycol and thoroughly mixed to obtain a homogenous dispersion.

2. Hydroxypropyl methylcellulose and polyvinylpyrrolidone were added in water and mixed thoroughly to obtain a uniform dispersion.
3. The dispersion of step 1 was added to the dispersion of step 2 with stirring to obtain the final sub coat dispersion.
4. Core tablets obtained above were loaded in Freund Hi-Coater and coated with the final dispersion of step 3 till the desired weight build up was achieved, followed by drying if required.

B. Enteric coating of sub-coated tablet involved the following steps-

1. Triacetin was dispersed in part of acetone followed by addition of HPMC Phthalate and continuous stirring till a clear solution was obtained.
2. Color, titanium dioxide and talc were added to the remaining part of acetone and thoroughly mixed to obtain a uniform dispersion.
3. Dispersion of step 2 was added to the solution of step 1 with continuous stirring to obtain the final coating dispersion.
4. Sub coated tablets were loaded in Freund Hi-Coater and coated with the final dispersion of step 3 till the desired weight buildup was achieved, followed by drying wherever required.

## WE CLAIM:

1. A method for the preparation of stable pharmaceutical composition of rabeprazole wherein the core comprises rabeprazole, low viscosity hydroxypropylcellulose and at least one antioxidant (s).
2. The method according to claim 1 wherein core further comprise polyvinylpyrrolidone.
3. The method according to claim 1 wherein low viscosity hydroxypropylcellulose is selected from Klucel® E, Klucel® G, Klucel® J and Klucel® L.
4. The method according to claim 3 wherein low viscosity hydroxypropylcellulose is Klucel® L.
5. The method according to claim 1 wherein low viscosity hydroxypropylcellulose comprises at least 10% by weight of the total core weight.
6. The method according to claim 1 wherein antioxidant(s) may be selected from the group consisting of lipophilic or inorganic antioxidants and the like.
7. The method according to claim 6 wherein antioxidant is butylated hydroxy toluene and/or butylated hydroxy anisole.
8. The method according to claim 1 wherein antioxidant(s) comprises from about 0.02% to about 0.2% by weight of the total core weight.
9. The method according to claim 2 wherein polyvinyl pyrrolidone is selected from the grades PVP K-15, K-25, K-30, K-60 and K-90.
10. The method according to claim 9 wherein polyvinylpyrrolidone is PVP K-30.
11. The method according to claim 2 wherein polyvinylpyrrolidone comprises from about 0.5% to about 5% by weight of the total core weight.
12. The method according to claim 1 wherein core is selected from tablet, granule, capsule and the like.
13. The method according to claim 12 wherein the core is a tablet.

14. The method according to claim 13 wherein tablet is prepared by wet granulation method, dry granulation or direct compression method.
15. The method according to claim 14 wherein tablet is prepared by direct compression technique.
16. The method according to claim 1 wherein core is coated with a sub coat layer and an enteric coat layer.
17. The method according to claim 16 wherein antioxidant(s) is incorporated in the sub coat layer.
18. The method according to claim 16 wherein sub coat layer comprises of film forming agent(s).
19. The method according to claim 18 wherein film forming agent is selected from the group consisting of microcrystalline cellulose, carageenan, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol, xanthan gum and the like.
20. The method according to claim 19 wherein film-forming agent is hydroxypropyl methylcellulose.
21. The method according to claim 16 wherein enteric coat layer comprises of an enteric polymer (s).
22. The method according to claim 21 wherein enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L30 D-55, Eudragit® L 100, Eudragit® S 100; and mixtures thereof.
23. The method according to claim 22 wherein enteric polymer is hydroxypropyl methylcellulose phthalate.
24. The methods according to claim 16 wherein sub coat and enteric coat layers are applied as a solution/ suspension.

25. The method according to claim 24 wherein solution/suspension is prepared in solvents selected from methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.

26. The methods according to claim 16 wherein coating is applied using hot melt technique.

27. A method for the preparation of stable pharmaceutical composition of rabeprazole wherein the core comprises rabeprazole, low viscosity hydroxypropylcellulose and at least one antioxidant, as described and illustrated by the examples therein.

Dated this **28TH** day of **February, 2003.**

**For Ranbaxy Laboratories Limited**

**(Sushil Kumar Patawari)**
**Company Secretary**

## ABSTRACT

A method for stabilizing rabeprazole with low viscosity hydroxypropylcellulose and antioxidant, and pharmaceutical compositions thereof is disclosed.